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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/485,601	05/04/00	STRITTMATTER S	OCR-842

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EXAMINER	
KERR,K	
ART UNIT	PAPER NUMBER
1652	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Supplemental Office Action Summary	Application No. 09/485,601	Applicant(s) STRITTMATTER, STEPHEN M.	
	Examiner Kathleen M Kerr	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *23 April 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-13,17 and 21-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-13,17 and 21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. The following action is a supplemental Office action added to the record for clarity after an interview with Applicants' representative on August 1, 2001 (see Paper No. 12 for summary). The instant action is a complete response to Applicants' response (Paper No. 10) to the first Office action on the merits (Paper No. 9); all arguments presented previously in Paper No. 11 (a final rejection in response to Paper No. 10) have been incorporated herein for completeness of the instant action. Applicants need *only* respond to the instant Office action to be fully responsive in the prosecution of the instant case.

Applicants filed a response on April 23, 2001 (Paper No. 10). Said response amended the specification and Claims 1, 6, 8, 12, and 17, canceled Claims 3-5, 14-16, and 18-20, and added new Claims 21-30. The Examiner notes that amendments to Claims 12 and 17 converted said claims into method claims from their original product claims.

Claims 1, 2, 6-13, 17, and 21-30 are pending in the instant application and will be examined herein.

Priority

2. As previously noted, Applicant is granted the benefit of priority for the provisional application 60/055,268 filed on August 13, 1997 and the internationally filed application PCT/US98/16794 filed on August 12, 1998 as requested in the declaration.

Also as previously noted, the subject matter of Claims 8 and 17 was not disclosed in the provisional application and, thus, is granted a priority date of August 12, 1998 for the

international filing. The subject matter of all other claims was disclosed in the provisional application and is granted a priority date of August 13, 1997 for the provisional application.

Drawings

3. Previously, the drawings were considered informal. Applicants' response to the previous Office action included the filing of new drawings. Said new drawing are also considered informal for the reasons detailed in the copy of PTO Form 948 attached to Paper No. 11. Appropriate correction is required prior to allowance.

Withdrawn - Objections to the Specification

4. Previous objection to the title (item 6 in Paper No. 9) for not being adequately descriptive of the claimed subject matter is withdrawn by virtue of Applicants' amendment.

5. Previous objection to the specification for lacking an abstract of the disclosure (item 7 in Paper No. 9) is withdrawn by virtue of Applicants' amendment.

6. Previous objection to the specification for lacking specificity on page 13, lines 20-28, which discloses particular amino acid residues of a protein, rho, (item 8 in Paper No. 9) is withdrawn by virtue of the Examiner's reconsideration in view of Applicants' arguments.

7. Previous objection to the specification for the use of undefined abbreviations (item 9 in Paper No. 9) is withdrawn by virtue of Applicants' amendment to the specification.

Withdrawn - Objections to the Claims

8. Previous objection of Claims 1, 2, 6-11 for containing non-elected subject matter (item 10 in Paper No. 9) is withdrawn by virtue of Applicants' amendment to the instant claims.

9. Previous objection to Claim 6 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, (item 11 in Paper No. 9) is withdrawn by virtue of Applicants' amendment to the instant claim.

Maintained - Claim Rejections - 35 U.S.C. § 112, second paragraph

10. Previous rejection of Claims 1, 2, 6, and 9-12 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "rho protein inhibitor" (item 12 in Paper No. 9) is maintained. As previously noted, in the instant specification, rho inhibitors are described as many things (see instant specification, page 10) including inhibitors of rac, cdc42, or other proteins in the GTP-binding family. The inclusion of the phrase "in amounts effective to inhibit rho or rac" only serves to further confuse the term; are only rho and rac inhibitors included in the metes and bounds of the claim or are all the GTP-binding family members, such as found in the instant specification on page 10, included?

Applicants present no arguments traversing the rejection; Applicants amended Claim 1, which amendment does not clarify the claim as noted above. Appropriate definition of the metes and bounds of the instant claim, particularly of the term "rho protein inhibitor", is required.

11. Previous rejection of Claims 8 and 17 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term C2/C3 inhibitor (item 13 in Paper No. 9) is maintained. As previously

noted, the structure of a C2/C3 chimeric *C. botulinum* construct is not clear. Applicants' amendment inserts required vague activities of the C3 portion of the chimeric protein.

Applicants present no arguments traversing the rejection; Applicants amended Claim 8, which amendment does not clarify the claim as noted above. Appropriate definition of the metes and bounds of the instant claim, particularly of the C2/C3 construct, is required. The Examiner suggests the inclusion of the specific enzymatic activity of the C3 fragment, namely specific ADP-ribosylation of rho (see instant specification, page 4, first paragraph).

Maintained - Claim Rejections - 35 U.S.C. § 112, first paragraph

12. Previous rejection of Claims 1, 2, and 6-11 under 35 U.S.C. § 112, first paragraph, enablement, (item 14 in Paper No. 9) is maintained. Applicants' arguments have been fully considered, but are not deemed persuasive for the following reasons.

Applicants argue that DRG neurons are central or peripheral confirming the scope of Applicants' invention and demonstrating *in vivo* efficacy. However, for examples using DRG neurons *in vitro* to effectively confirm the claimed scope, said examples must a) use an art-accepted or otherwise validated CNS model system and b) *in vitro* data must be reasonably predictive of *in vivo* results. While DRG neurons may be a reasonable model system for CNS, the predictability of *in vivo* results from *in vitro* data is not supported in either the specification or the art. The disclosure of Lehmann *et al.* specifically perform their experiments in an *in vivo* model to test for results *in vivo* (see page 7541, right column); no assumptions are made that the *in vitro* data presented by Lehmann *et al.* are indicative of *in vivo* results. Additionally, Bartsch *et al.* (Neuron (1995) 15:1375-1381) specifically teach that "regeneration experiments in the

living animal are the crucial tests of whether a certain molecule plays a physiological role in determining the extent of axonal regeneration" (see page 1379, left column). In fact, the *in vitro* experiments of Bartsch *et al.*, using several CNS *in vitro* model systems, are **not** indicative of their *in vivo* results. Therefore, it is clear that the instant specification, coupled with the prior art, has not enabled any of the scope of the instant claims using *in vitro* data since all the claims require *in vivo* results for enablement.

It is clear, however, from the post-filing date reference of Lehmann *et al.*, that *in vivo* treatment of optic nerves in adult rats with C3 inhibitor from *C. botulinum* promotes axon regeneration (see Abstract). Therefore, although this portion of scope of the instant claims was not predictably enabled by the instant specification at the time of filing, data support Applicants' assertion that some scope of the instant claims are enabled (i.e. function as predicted in view of the *in vitro* results). With this in mind, the ***only*** scope of the instant claims that is enabled, in view of the predictive value of the instant specification in combination with the post-filing date art supporting said prediction, is the following:

> A method for promoting optic nerve growth in a patient ... comprising topically administering C3 (or C2/C3 having the enzyme activity of C3) in an amount effective to stimulate neurite outgrowth.

With this view of enablement in mind, only portions of Claims 7 and 8 pertain to allowable subject matter. The inclusion of limitations to the optic nerve portion of the CNS is required because of the very low predictive value between different axons of the CNS, especially between those axons considered sensory (to some extent peripheral) and central (brain). The inclusion of limitations to administration routes is required because of the very low predictive value between a simple administration route, such as topical (as found in Lehmann *et al.*), and a significantly

more complex route, such as injection, as contemplated in the instant specification concerning "mechanical routes" (see pages 10-11, bridging paragraph). Applicants are reminded that for all amendments to the claims, clear support must be cited (using page and line number) in the specification as originally filed for any amended subject matter.

With respect to the use of the instant methods of treat specific injuries, such as spinal cord injury, stroke, and brain injury (Claims 9-11), neither the *in vitro* models in the specification nor the limited, proven experiments of the Lehmann *et al.* post-filing date reference adequately enable the claims since these injuries are complex and methods of regeneration of all types of CNS axons is wholly unpredictable.

With respect to using other rho-specific inhibitors, the Examiner maintains the position that the enablement of the instant claims relies on having reasonably predictive data to support the claimed methods (none of which is presented in the instant application), and no such data has been presented for any other rho-specific inhibitors. Moreover, the mechanism of axon regeneration in optic nerves, not to mention CNS, has not been fully established in any art to date. Therefore, the predictability of using other rho-specific inhibitors in the claimed methods is very small. This same argument follows considering the broader rho-subfamily-specific inhibitors which would include inhibitors of rac and cdc42.

13. Previous rejection of Claims 1-2, 6, and 9-12 under 35 U.S.C. 112, first paragraph, written description, (item 15 in Paper No. 9) is maintained. The instant claims are drawn to methods of using rho protein inhibitors and, the Examiner maintains, Applicants have not described a representative number of species in such a large genus. Applicants' arguments have been fully considered but are not considered persuasive for the following reasons.

Applicants argue that, upon the availability of the human genome, all the GTP-binding proteins are now identified. The Examiner disagrees with this generalization. While the human genome may be fully sequenced, the functionality of all its possible genes has not nearly been completely analyzed. Moreover, no limitation of human rho proteins and inhibitors thereof is included in the instant claims so that availability of the *human* genome is not wholly applicable. The Examiner also notes that, even if all GTP-binding proteins were identified, this is not the case of the genus of *all* inhibitors of GTP-binding protein. The Examiner has noted Nobes *et al.*, as supplied by Applicants, and has failed to identify any evidence in Nobes *et al.* to convince the Examiner that the disclosure of a single rho protein inhibitor effectively describes the broad genus. For all of the above reasons, the instant rejection is maintained.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

14. Previous rejection of Claim 12 under 35 U.S.C. § 102(b) as being anticipated by Morii *et al.* (item 6 in Paper No. 9) is withdrawn by virtue of Applicants' amendment changing Claim 12 from a product claim into a method claim, which method claim is not anticipated by Morii *et al.*

Maintained - Claim Rejections - 35 U.S.C. § 102

15. Previous rejection of Claim 13 under 35 U.S.C. § 102(b) as being anticipated by Morii *et al.* is maintained. Applicants' response describes an amendment to Claim 13; however, no such amendment is set forth. Applicants present no other arguments. The instant rejection is, therefore, maintained.

Withdrawn - Claim Rejections - 35 U.S.C. § 103

16. Previous rejection of Claim 17 under 35 U.S.C. § 103(a) as being unpatentable over Barth *et al.* in view of Morii *et al.* (item 17 in Paper No. 9) is withdrawn in view of Applicants' amendment changing Claim 17 from a product claim into a method claim, which method claim is not obviated by the combination of Barth *et al.* and Morii *et al.*

NEW REJECTIONS

The following are (a) reiterations rejections from above newly applied to newly added or amended claims or (b) newly developed rejections necessitated by Applicants' amendments.

Claim Objections

17. Claims 12 and 17 are objected to for a typographical errors for the following reasons:

a) In Claim 12, line 5, "5n" is misspelled – the correct spelling is ---in---.

b) In Claim 17, line 2, "*botulimun*" is misspelled – the correct spelling is ---*botulinum*---as set forth in other claims and throughout the specification.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 8 and 24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 24 depends from itself and, thus, is wholly unclear;

Claim 8 is unclear by virtue of its dependency on Claim 24 without correcting the defect. Appropriate clarification is required.

19. Claims 12, 13, and 25-27 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 12, it is unclear how a rho protein can be an inhibitor of itself. Appropriate clarification is required.

20. Claims 21-23 and 25-27 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "rho protein inhibitor" as set forth above and in a previous Office action for Claims 1, 2, 6, and 9-12.

21. Claims 23 and 28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "a *C. botulinum* C3 inhibitor" is confusing because throughout the instant specification and the claims, the *C. botulinum* C3 protein is called and exoenzyme. Moreover, the article "a" indicates that the claims encompass *any* C3 protein; however, the metes and bounds of such a genus are undefined in the instant specification. Appropriate clarification is required.

22. Claim 30 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term C2/C3 inhibitor as set forth above and in a previous Office action for Claims 8 and 17.

23. Claim 30 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In line 1, the term "the composition" has no antecedent basis. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

24. Claims 12, 17, and 21-30 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, as set forth above and in a previous Office action for Claims 1, 2, and 6-11.

25. Claims 21-22 and 25-27 are rejected under 35 U.S.C. § 112, first paragraph, written description, as set forth above and in a previous Office action for Claims 1-2, 6, and 9-12.

Summary of Pending Objections/Rejections

26. The following is a summary of the pending objections/rejections of the instant claims which must be addressed in response to the instant Office action:

a) Claims 12 and 17 are objected to for a typographical errors

b) Claims 1, 2, 6, 9-12, and 21-23 and 25-27 stand rejected under 35 U.S.C. § 112, second paragraph, for the term "rho protein inhibitor".

c) Claims 8, 17, and 30 stand rejected under 35 U.S.C. § 112, second paragraph, for the term C2/C3 inhibitor.

d) Claims 8 and 24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because Claim 24 depends from itself and Claim 8 depends from Claim 24.

e) Claims 12, 13, and 25-27 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because, as found in Claim 12, it is unclear how a rho protein can be an inhibitor of itself.

f) Claims 23 and 28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for term "a *C. botulinum* C3 inhibitor".

g) Claim 30 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "the composition" which has no antecedent basis.

h) Claims 1, 2, 6-12, 17, and 21-30 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement.

i) Claims 1-2, 6, 9-12, 21-22 and 25-27 stand rejected under 35 U.S.C. 112, first paragraph, written description.

j) Claim 13 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Morii *et al.*

Conclusion

27. Claims 1, 2, 6-13, 17, and 21-30 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
August 8, 2001

PONNATHAPU ACHUTAMURTHY
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